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October 10, 2000

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

We would like to bring to your attention recent post-marketing reports of adverse events in patients receiving ENBREL® (etanercept). Rare cases of central nervous system disorders, including demyelinating disorders such as multiple sclerosis, myelitis, and optic neuritis, have been reported in patients with rheumatoid arthritis who have received ENBREL therapy. Although the causal relationship to ENBREL therapy remains unclear, other tumor necrosis factor (TNF) antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity[1,2]. Prescribers should exercise caution in considering the use of ENBREL in patients with preexisting or recent-onset central nervous system demyelinating disorders.

In addition, rare cases of pancytopenia, including aplastic anemia, some with a fatal outcome, have been reported in patients with rheumatoid arthritis who have received ENBREL therapy. Although the majority of patients who have developed pancytopenia on ENBREL therapy had recent or concurrent exposure to other anti-rheumatic medications known to be associated with myelosuppression (e.g., methotrexate, leflunomide, azathioprine, and cyclophosphamide), some patients had no recent or concurrent exposure to such therapies. Cases of pancytopenia occurred as early as 2 weeks after initiating ENBREL therapy. The causal relationship to ENBREL therapy remains unclear. Patients should be advised that if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on ENBREL, they should seek immediate medical attention. If significant hematologic abnormalities are identified, consideration should be given to discontinuation of ENBREL therapy.

As a result of these reports, the prescribing information for ENBREL (etanercept) has been revised to include the following new Warning statements.

WARNINGS

Neurologic Events

Rare cases of central nervous system demyelinating disorders have been described in spontaneous adverse event reports (see **ADVERSE REACTIONS**). The causal relationship to ENBREL therapy remains unclear. However, while no clinical trials have been performed evaluating ENBREL therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity. Prescribers should exercise caution in considering the use of ENBREL in patients with preexisting or recent-onset central nervous system demyelinating disorders.

Centocor

October 18, 2001

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Centocor, Inc. would like to inform you of important new safety information for REMICADE® (infliximab). Upon review of preliminary results of its ongoing phase 2 trial in 150 patients with moderate to severe (NYHA class III-IV) congestive heart failure (CHF), higher incidences of mortality and hospitalization for worsening heart failure were seen in patients treated with REMICADE, especially those treated with the higher dose of 10 mg/kg. Seven of 101 patients treated with REMICADE died compared to no deaths among the 49 patients on placebo.

In this trial, stable but symptomatic patients with NYHA Class III-IV CHF were treated with 3 infusions of REMICADE 5 mg/kg, REMICADE 10 mg/kg, or placebo over 6 weeks. REMICADE is a biological therapeutic product indicated for the treatment of rheumatoid arthritis and Crohn's disease.

Centocor, in consultation with FDA, is alerting physicians to these potential adverse effects of REMICADE in patients with CHF. At present, there are insufficient data to determine optimal patient management. However, based on these preliminary findings, and pending additional data, physicians should consider the following precautionary measures.

For patients with rheumatoid arthritis or Crohn's disease being considered for therapy with REMICADE:

- Do not initiate therapy in patients with congestive heart failure.

Patients with CHF currently receiving chronic REMICADE treatment for rheumatoid arthritis or Crohn's disease should be reevaluated.

- Treatment should be discontinued in patients whose CHF is worsening.

- Treatment discontinuation should be considered in patients with stable concomitant CHF, especially in those who have not had a significant clinical response to REMICADE therapy. If a decision is made to continue treatment, cardiac status should be closely monitored.

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EC warns against concurrent Kineret and Enbrel use

The safety information in the European labelling for two rheumatoid arthritis products, Amgen's Kineret (anakinra) and Amgen/Wyeth's Enbrel (etanercept), has been strengthened to warn against concurrent use of the two products.

The move follows the results of a 242-patient Amgen-sponsored clinical trial which showed a higher incidence of serious infection and neutropenia in rheumatoid arthritis patients taking the two products together compared with patients receiving Enbrel alone and higher than observed in previous trials of Kineret. The study also failed to show any therapeutic benefit of the combination treatment over etanercept alone.

The EMEA says the label changes were approved by the CPMP late last month through a type II variation and the revised summaries of product characteristics are being forwarded to the EC Commission for implementation.

The special warnings and special precautions for use section of Kineret's label will now read: "Concurrent administration of Kineret and etanercept has been associated with an increased risk of serious infections and neutropenia compared to etanercept alone. This treatment combination has not demonstrated increased clinical benefit. The concurrent administration of Kineret and etanercept or other TNF antagonists is not recommended." Similar changes have been made to Enbrel's label.

Kineret and Enbrel act in different ways to treat rheumatoid arthritis: Kineret is a recombinant form of the human interleukin-1 receptor antagonist, whereas Enbrel inhibits TNF-alpha. Because both IL-1 and TNF are pro-inflammatory cytokines, the theory was that using a two-pronged approach might provide greater benefit than either drug alone. If it had been proven, this would have given a extra niche market for anakinra which is struggling against the perception that it is less effective than the anti-TNF products.

But concerns over the potential pitfalls of combination therapy are not new. Back in 2001, when anakinra was under discussion for approval by the US FDA's arthritis advisory committee, five out of nine panel members wanted its use in combination with anti-TNF drugs contraindicated because of the serious infection risk. It noted the results of a small 58-patient open-label trial where anakinra was added to Enbrel therapy in which 7% of patients developed serious infections and 3% neutropenia (*Scrip* No 2697, p 18).

When it approved anakinra, the FDA decided against contraindicating the product in combination with Enbrel but included details of this study and stated that anakinra's use in combination with TNF-blockers had not been established in the label's Warnings section.

These results have now been replicated on a larger scale. In the 24-week randomised controlled trial, 242 rheumatoid arthritis patients who had not previously been treated with biologic agents and who were taking background methotrexate received 25mg of Enbrel biweekly alone or with 100mg/day of Kineret. 7% of patients in the combination group experienced a serious infection and neutropenia also occurred, the EMEA says. The incidence of neutropenia and serious infection was higher than in the Enbrel-alone group and higher than observed in previous trials where Kineret was used alone.

New Japan Iressa trial planned

AstraZeneca is planning a new large-scale trial with its anticancer, Iressa (gefitinib), in non-small-cell lung cancer (NSCLC) patients in Japan to investigate in more detail the lung disorders associated with the product.

The study may involve around 5,000 advanced NSCLC patients and should start within the next few months, although final design and protocol details are still being worked out. Analyses of the pulmonary disorders seen with the product in Japan, mostly interstitial pneumonia, have been retrospective so far, and the company sees a need for a new prospective study, its Japanese subsidiary told *Scrip*.

Iressa, the first epidermal growth factor receptor inhibitor to reach the market, was launched in Japan (its first market worldwide) last July. By the end of January, it had been associated with 473 cases of lung disorders, including at least 173 deaths, newly updated figures show. The product had by that time been used in around 23,500 NSCLC patients in Japan, the company noted at a Tokyo media update on the problems, given by two local cancer specialists.

Both the company and the Ministry of Health, Labour and Welfare have set up committees to review the side-effects, which have already recommended stricter use precautions and monitoring. Measures recommended by the ministry late last year included limiting use to trained oncologists, hospitalisation during the first four weeks of treatment, and tighter family/patient consent procedures (*Scrip* No 2811/12, p 19). These and earlier actions now appear to be having some positive effect on the number of reported ADRs.

The US FDA recently requested more time for its priority review of Iressa. The NDA review will now be completed on May 5th.